Preventive Cardiology
Beyond Statins for Cardiovascular Risk Reduction

M. Wesley Milks, MD, FACC
Assistant Professor of Clinical Medicine
Division of Cardiovascular Medicine
Department of Internal Medicine
The Ohio State University Wexner Medical Center

Introduction

- Objectives
  1. Identify clinical scenarios in which statins and/or non-statin lipid lowering treatments are indicated
  2. Describe the mechanism of action of and indications for PCSK9 inhibitors, SGLT2 inhibitors, and high dose omega-3-polyunsaturated fatty acids

- No competing interests /financial relationships to disclose
- I will discuss what is currently off-label use of icosapent ethyl (Vascepa®)
- Branded Rx/OTC products shown: not an endorsement

Outline

- Recent history of and important concepts in clinical lipidology
- New ACC/AHA Blood Cholesterol guidelines: goals are back
- PCSK9 inhibition: when and how?
- SGLT2 inhibition: inducing glycosuria improves outcomes
- Marine omega-3 polyunsaturated fatty acids: fishy or not?
- Other “nutraceuticals”: is there a role?
2013 ACC/AHA Guidelines

Step 1: Decide whether there is an indication for a statin
Next steps: unclear
- Is there a goal LDL-C to achieve?
- What is the role of non-statins?
- The LDL "hypothesis": to what extent does non-statin LDL-C lowering reduce risk?


Major ASCVD risk factors (HALFS)
- HTN
- Age (Mz45, Fz55 y)
- Low HDL
- FMHx early CHD (Mz55, Fz65)
- Smoking

Risk Category Non-HDL-C goal LDL-C goal
- Low < 130 mg/dl < 100
- Moderate < 130 < 100
- High < 130 < 100
- Very High < 100 < 70

ASCVD, or [Diabetes mellitus + end organ damage]

NLA Part 1 / Part 2 (2015)

On-Treatment LDL Cholesterol vs. events
- Reduce LDL-C or non-HDL-C by ~40 mg/dl
- Lower (RRR) ASCVD by ~20%

• We live in an LDL-C paradigm. Why?

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>N (IMACE)</th>
<th>N (Total)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 100 mg/dl</td>
<td>≥ 130 mg/dl</td>
<td>1,877</td>
<td>10,419</td>
<td>1.21 (1.13-1.29)</td>
</tr>
<tr>
<td>≥ 100 mg/dl</td>
<td>&lt; 130 mg/dl</td>
<td>467</td>
<td>2,673</td>
<td>1.02 (0.92-1.12)</td>
</tr>
<tr>
<td>&lt; 100 mg/dl</td>
<td>≥ 130 mg/dl</td>
<td>283</td>
<td>1,435</td>
<td>1.72 (1.17-2.50)</td>
</tr>
<tr>
<td>&lt; 100 mg/dl</td>
<td>&lt; 130 mg/dl</td>
<td>2,760</td>
<td>23,426</td>
<td>1.00 (Reference)</td>
</tr>
</tbody>
</table>

- Statin-treated patients who reached goals of LDL-C, non-HDL-C, both, or neither
- When discordant, non-HDL-C predicts major CV events better than LDL-C
- HRs adjusted for sex, age, smoking, DM, SBP, and trial


2016-2017 ACC Expert Consensus

• Role of non-statin therapies for LDL-C lowering in management of ASCVD risk

Step 1: Decide whether there is an indication for a statin
Step 2: Consider non-statin therapies
Step 3: Recognize non-statin indications

- Consider adherence, statin tolerance, control of risk factors
- Consider percentage LDL-C & non-HDL-C reduction and level achieved
- Consider ezetimibe, bile acid sequestrants, PCSK9i
Preventive Cardiology
Beyond Statins for Cardiovascular Risk Reduction

Kelly M. Bartsch, PharmD, BCPS, CLS
Specialty Practice Pharmacist - Ambulatory Care
The Ohio State University Wexner Medical Center

Statins
- Dosing + Effects:
  - Potency varies by statin and dose
    - High intensity: >50% ↓LDL-C
    - May also decrease TRG and HDL
  - PO formulations
  - Once daily administration*
  - Newer agents can be taken at any time of day
  - Pleiotropic effects
  - Adverse Effects:
    - Myalgias, GI upset
  - Drug interactions
  *exception: fluvastatin

Ezetimibe
- Mechanism
  - Blocks NPC1L1
  - Inhibits enteric cholesterol absorption
  - (Statins increase chol. absorption)
  - Dosing & effect
    - 10 mg PO daily
    - Expect 15-25% ↓LDL-C

Statins – Potency + Lipophilicity

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Simvastatin</th>
<th>Fluvastatin</th>
<th>Pitavastatin</th>
<th>Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>20mg</td>
<td>20mg</td>
<td>10mg</td>
<td>40mg</td>
<td>1mg</td>
<td></td>
</tr>
<tr>
<td>Mod.</td>
<td>40mg</td>
<td>40mg</td>
<td>20mg</td>
<td>80mg</td>
<td>4mg</td>
<td>20mg</td>
</tr>
<tr>
<td>High</td>
<td>80mg</td>
<td>80mg</td>
<td>(60mg)</td>
<td>10mg</td>
<td>10mg</td>
<td>20mg</td>
</tr>
</tbody>
</table>

Lipophilic: Atorvastatin, lovastatin, simvastatin
Hydrophilic: Pravastatin, rosuvastatin, fluvastatin

Ezetimibe
- Dietary cholesterol
- Bilirubin cholesterol
- Enteroocytes

\[
\text{Mevalonic acid} \rightarrow \text{HMG-CoA} \rightarrow \text{Acetyl-CoA} \rightarrow \text{ATP citrate lyase} \rightarrow \text{Acetyl-CoA} \rightarrow \text{HMG-CoA} \rightarrow \text{Lipophilic}
\]

\[
\text{Cholesterol} \rightarrow \text{Ezetimibe} \rightarrow \text{Lipophilic}
\]

\[
\text{Statins} \rightarrow \text{Lipophilic}
\]

\[
\text{Ezetimibe} \rightarrow \text{Lipophilic}
\]
**Ezetimibe**

- Adverse effects
  - Respiratory tract symptoms (4% vs. 2% placebo)
  - Transaminase elevations with statins (1-2%)
  - GI symptoms comparable to placebo

**IMPROVE-IT**

- Outcomes from non-statin driven LDL-C reduction
  - 18,144 patients with acute coronary syndrome
  - LDL-C at baseline: 50 to 125 mg/dl
  - Randomization: simvastatin 40 mg + [ezetimibe 10 mg OR placebo]

- Primary end point composite: cardiovascular death, nonfatal MI, UA requiring hospitalization, coronary revascularization (≥ 30 d after randomization), nonfatal CVA

- Median follow up 6 years
- Outcome: HR 0.936 (95% CI 0.89-0.99)
**PCSK9 inhibitors**

**Mechanism, dosing, and adverse effects**

- **Mechanism**
  - Human IgG1/2 mAb that inhibits proprotein convertase subtilisin/kexin type 9 binding to LDLR
  - $T_{1/2}$ 17-20 days (alirocumab) or 11-17 (evolocumab) days

- **Adverse effects**
  - Injection site reactions (7% vs. 5% placebo)
  - Nasopharyngitis, flu-like reaction, myalgias, new onset DM similar to placebo
  - Antibody formation
  - Rare serious allergic reactions

**FOURIER: Outcomes from non-statin driven LDL-C reduction**

- Enrollment: 27,564 patients with ASCVD, LDL-C $\geq$ 70 mg/dl receiving statin therapy
- Treatment: evolocumab 140 mg q2wk or 420 mg q4wk vs. placebo
- Outcome: [CV death, MI, CVA, hospitalization for UA, coronary revascularization]
- Follow up: median 2.2 years
PCSK9 inhibitors

FOURIER: Outcomes from non-statin driven LDL-C reduction

- Outcome: [CV death, MI, CVA, hospitalization for UA, cor. revasc.]
- Follow up: median 2.2 years


PCSK9 inhibitors

FOURIER: Outcomes from non-statin driven LDL-C reduction

- Adverse events: no significant difference (incl. new DM, neurocognitive events) except injection site reactions (2.1% vs. 1.6% placebo)


PCSK9 inhibitors

ODYSSEY OUTCOMES: Outcomes from non-statin driven LDL-C reduction

- Enrollment: 18,924 patients with acute coronary syndrome
- Uncontrolled cholesterol: LDL-C ≥ 70 or non-HDL-C ≥ 100 mg/dl on high-intensity or maximum-tolerated statin
- HR 0.85 (95% CI 0.78-0.93, P<0.001)


PCSK9 inhibitors

ODYSSEY OUTCOMES: Outcomes from non-statin driven LDL-C reduction

- Treatment: alirocumab vs. placebo (targeted LDL-C 25 to 50 mg/dl)
- Outcome: [CHD death, nonfatal MI, ischemic CVA, UA req. hospitalization]
- Follow-up median 2.8 years
- HR 0.85 (95% CI 0.78-0.93, P<0.001)

**PCSK9 inhibitors**

Outcomes from non-statin driven LDL-C reduction

<table>
<thead>
<tr>
<th></th>
<th>FOURIER</th>
<th>ODYSSEY OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>CV death, MI, stroke, hospitalization</td>
<td>CHD death, non-fatal MI, fatal or non-fatal</td>
</tr>
<tr>
<td>(composite)</td>
<td>for unstable angina, or cor.</td>
<td>ischemic stroke, or UA requiring hospitalization</td>
</tr>
<tr>
<td>Treatment vs. placebo</td>
<td>9.8% vs. 11.3%</td>
<td>9.5% vs. 11.1%</td>
</tr>
<tr>
<td>Median follow up</td>
<td>2.2 years</td>
<td>2.8 years</td>
</tr>
<tr>
<td>HR</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>NNT</td>
<td>67</td>
<td>64</td>
</tr>
</tbody>
</table>

**PCSK9 inhibitors: what about cost?**

<table>
<thead>
<tr>
<th>SUGGESTED COST-EFFECTIVE ANNUAL PRICE ($100,000-150,000 PER QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approx. US Price (mid-2018)</td>
</tr>
<tr>
<td>Approx. Canadian Price (USD)</td>
</tr>
</tbody>
</table>

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**Recent History of Preventative Cardiology**

- LDL-C or non-HDL-C goals are optional. Non-statin are included again.
- Aren’t we due for a “fully updated” guideline??
• **Principles of the guideline**
  — Assess ASCVD risk in each age group
  — Emphasize adherence to healthy lifestyle


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At all levels: provide a "risk discussion" as it relates to the management plan


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• **Principles of the guideline**
  — Consider ASCVD risk "enhancers" when making treatment decisions

Clinical ASCVD

Yes

Very high risk?

- Multiple major ASCVD events (recent ACS, h/o MI, h/o CVA, PAD), OR
- Major ASCVD event + multiple high-risk conditions (age ≥ 65, FH, h/o PCI/CABG, DM, HTN, CKD, smoking, persistently elevated LDL ≥ 100, h/o CHF)

No

- High (or if >75 yrs, moderate or high [IIa]) intensity statin (I), or if not tolerated, moderate intensity statin
- If LDL-C ≥ 70 mg/dl, ezetimibe is reasonable

Metabolic syndrome and diabetes mellitus

- Metabolic syndrome: co-occurrence of cardiovascular risk factors
- Share mechanisms of type 2 diabetes mellitus

Outline

- Recent history of and important concepts in clinical lipidology
- New ACC/AHA Blood Cholesterol guidelines: goals are back
- PCSK9 inhibition: when and how?
- SGLT2 inhibition: inducing glycosuria improves outcomes
- Marine omega-3 polyunsaturated fatty acids: fishy or not?
- Other “nutraceuticals”: is there a role?
- Hormone sensitive lipase (HSL) mobilizes stored fat, breaking down TGs, freeing FAs
- More energy in bloodstream
- HSL is inhibited by insulin

- Lipoprotein lipase (LPL) cleaves TGs into free fatty acids (FFAs)
- “Clears” TG-rich particles from the circulation
- Less energy in bloodstream
- LPL is activated by insulin

- Hepatic VLDL production also occurs when increased circulating energy stores are needed
- VLDL production is inhibited by insulin

- VLDL can transfer its TG content to LDL
- TG-rich LDL is preferentially converted to small, dense LDL which is particularly atherogenic

- After VLDL and chylomicrons (CM) donate their lipid contents to end-tissues, they become VLDL or CM remnants
- Remnants are particularly atherogenic
Normal state
- Circulating VLDLs and CMs are kept to a minimum
- Energy is "cleared appropriately" from the bloodstream for utilization or storage

Diabetic dyslipidemia
- Increased serum triglycerides
- Decreased HDL-C
- Predominance of small dense LDL particles and VLDL/CM remnants

SGLT2 inhibitors
- Therapeutic glycosuria
  - Class currently includes canagliflozin, dapagliflozin, and empagliflozin
  - Mechanism
    - Prevent reabsorption of glucose by the kidneys
    - Net decrease in blood sugar
  - Dosing & effect
    - Oral agents with daily dosing
    - A1c lowering of 0.5-0.8%
  - Adverse effects
    - Hypotension
    - Urinary tract infections
    - Ketoacidosis
    - AKI
SGLT2 inhibitors

- Therapeutic glycosuria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Approximate effect of SGLT2 inhibitor treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>↓ 4 kg</td>
</tr>
<tr>
<td>Visceral adipose tissue mass</td>
<td>↓ 8%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↓ 4%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>↑ 6%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↑ 2%</td>
</tr>
</tbody>
</table>

Outline

- Recent history of and important concepts in clinical lipidology
- New ACC/AHA Blood Cholesterol guidelines: goals are back
- PCSK9 inhibition: when and how?
- SGLT2 inhibition: inducing glycosuria improves outcomes
- Marine omega-3 polyunsaturated fatty acids: fishy or not?
- Other “nutraceuticals”: is there a role?
**Omega-3 Fatty Acids**

- Mechanism of action – not well elucidated
  - Proposed: increased beta oxidation, inhibition of acyl-CoA, decreased hepatic production of VLDL, increased LPL activity
- Dosing & effect
  - For TG >500: dosed at 2g twice daily
  - Primary effect is to lower TG
  - DHA component can increase LDL
- Adverse effects
  - Prolongation of bleeding time
  - Fishy aftertaste or belching
  - Nausea

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**ω-3-poly-unsaturated fatty acids**

- DHA 22:6
- EPA 20:5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Approximate effect of ω-3 PUFA treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>↓5-14%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↓19-44%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>±</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↓6% - 125%</td>
</tr>
</tbody>
</table>

**Does treatment change outcomes?**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Endpoints / Mean Follow-up</th>
<th>Daily dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of 10 trials Aung et al. JAMA Cardiol 2018 (n=77,917) prior CHD, CVA, or high ASCVD risk</td>
<td>Any CHD (fatal/non-fatal) or major vascular events 4.4 years</td>
<td>Generally 1 g EPA/OM-3 FA</td>
<td>No effect</td>
</tr>
<tr>
<td>GISSI-Prevenzione Investigators Lancet 1999; (n=11,324) with recent MI (2x2 design also with statin)</td>
<td>Death, non-fatal MI, CVA 3.5 years</td>
<td>1 g EPA/OM-3 FA vs. Placebo</td>
<td>Benefit Composite RRR 10% Death RRR 14%</td>
</tr>
<tr>
<td>JELIS Yokoyama et al. Lancet 2007 (n=18,646) unselected hypercholesterolemic (Total-C &gt; 252 mg/dl) Japanese patients</td>
<td>Any CHD event (CHD death, SCD, total/non-fatal MI, UA, PCI, CABG) 4.6 years</td>
<td>Statin + [1.8 g EPA-OM-3 FA or Placebo]</td>
<td>Benefit Composite RRR 19% No difference in LDL</td>
</tr>
</tbody>
</table>

**REDUCE-IT**

- Enrollment: 8,179 patients with hypertriglyceridemia (135-499 mg/dl) and “controlled” LDL (41-100 mg/dl).
- Patients were (mean) 64 yrs, 71% male, BMI 30.8, most on statins
- Endpoint: [CV death, nonfatal MI, nonfatal CVA, coronary revascularization or UA]
- Treatment: icosapent ethyl (EPA only) 4 g/day (2 g bid with food) vs. placebo (mineral oil)
- Follow-up: 4.9 yrs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment (EPA)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>↓18.3% (-39 mg/dl)</td>
<td>↑2.2% (+4.5 mg/dl)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↓3.1% (-2.0 mg/dl)</td>
<td>↑10.2% (+7.0 mg/dl)</td>
</tr>
</tbody>
</table>


**REDUCE-IT**

What's the catch?

- Any adverse effects?
  - No difference in bleeding, including hemorrhagic stroke
  - Hospitalization for atrial fibrillation or flutter was 3.1% in EPA group vs. 2.1% placebo (p=0.0004).
- Is it just the triglyceride lowering?
  - ACCORD-Lipid: fenofibrate lowers TG but no change in outcome
  - AIM-HIGH, HPS2-THRIVE: niacin lowers TG but no change in outcome
- Will REDUCE-IT change practice?


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**ω-3-poly-unsaturated fatty acids**

### Antiarrhythmic or not?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCE-IT 2019</td>
<td>4 g/d EPA only</td>
<td>47% excess atrial fibrillation</td>
</tr>
<tr>
<td>Cochrane Review 2016</td>
<td>Varies (0.5 to &gt;5 g/d)</td>
<td>Marine: No difference arrhythmia; 21% arrhythmias</td>
</tr>
<tr>
<td>GISSI-HF (n=6,975) with HF</td>
<td>1 g/d mixed</td>
<td>No difference in atrial fibrillation; 9% mortality; 8% HF admissions</td>
</tr>
</tbody>
</table>

- Animal studies suggest DHA may have antiarrhythmic properties in AF


### Current Rx products and labeling

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade Name Composition</th>
<th>Dose</th>
<th>Labelled Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>eicosapentenoic acid</td>
<td>Vascoheart®</td>
<td>2 g bid with food</td>
<td>Significant hypertriglyceridemia (&gt;500 mg/dL) as adjust to diet and exercise</td>
</tr>
<tr>
<td>ω-3 acid ethyl esters</td>
<td>Lovaza® 50% EPA/40% DHA</td>
<td>4 g/d or 2 g bid +/- food</td>
<td>Significant hypertriglyceridemia (&gt;500 mg/dL) as adjust to diet and exercise; For use as an adjunct to simvastatin for hyper-TG</td>
</tr>
<tr>
<td>ω-3 carboxylic acids</td>
<td>Epamar® Mostly EPA</td>
<td>2-4 g/d +/- food</td>
<td>Significant hypertriglyceridemia (&gt;500 mg/dL) as adjust to diet and exercise</td>
</tr>
</tbody>
</table>


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**ω-3-poly-unsaturated fatty acids**

### Should I just buy OTC fish oil at the drug store?

**How to get 2 g EPA**

- **Vascopea®**
  - 700 mg EPA 240 mg DHA
- **Lovaza®**
  - 250 “omega-3”
    - 150 mg EPA
    - 110 mg DHA
- **Viva Naturals**
  - 700 mg EPA 600 mg DHA
- **Kirkland**
  - 360 mg EPA 300 mg DHA
- **Nature Made**
  - 400 mg EPA 260 mg DHA

"Nutraceuticals"

Doc, is it OK if I take…?

- Certain nutraceuticals…alone or in combination with each other, as well as ezetimibe, might be considered as an alternative or add-on therapy to statins, although there is still insufficient evidence available with respect to long-term safety and effectiveness.

"Nutraceuticals" and lifestyle changes

<table>
<thead>
<tr>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>Berberine</td>
</tr>
<tr>
<td>Artichoke</td>
</tr>
<tr>
<td>Garlic</td>
</tr>
<tr>
<td>Green tea</td>
</tr>
</tbody>
</table>

A Case Study

34-year-old man with family history of heart disease is interested in lowering his cholesterol "naturally" (despite low 10-year est. ASCVD risk).
Take Home Points

- Recent history of and important concepts in clinical lipidology
  - Please consider non-HDL-C as well as LDL-C lowering, especially in hypertriglyceridemics
  - New ACC/AHA Blood Cholesterol guidelines
  - Goal atherogenic cholesterol levels are both motivating and evidence based
  - PCSK9 inhibition: when and how?
    - FH or ASCVD and LDL-C > 70 or non-HDL-C > 100 mg/dl

Take Home Points

- SGLT2 inhibition: inducing glycosuria improves outcomes
  - Discuss ASCVD benefits of DM drugs with PCP, endocrine
  - Marine omega-3 polyunsaturated fatty acids and other “nutraceuticals”
    - May have a role, consider in statin intolerance/refusal